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August 14, 2006

TO: United States Patent and Trademark Office
Mail Stop Appeal Brief - Patents
Fax # 571-273-8300

RE: Art Unit 1616
Serial No.: 09/901,979
Examiner: A. Pryor

FROM: Norris McLaughlin & Marcus, P.A.
Kurt G. Briscoe

ATTORNEY DOCKET NO.: 100717-477 / Bayer 8890.4 KGB

MESSAGE:

Forwarded herewith are the following

1) **Appellants' Corrected Brief of Appeal (17 pages)**
2) **Declaration of Martin Kugler dated September 26, 2002 (7 pages)**
3) **Declaration of Martin Kugler dated December 15, 2005 (5 pages)**

By Jennifer Archer Date August 14, 2006
Jennifer Archer

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Date: August 14, 2006

By: Jennifer Auch

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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

APPLICANTS	:	LUTZ HEUER ET AL.
SERIAL NO.	:	09/901,979
FILED	:	July 10, 2001
FOR	:	MICROBICIDAL COMPOSITIONS
ART UNIT	:	1616
EXAMINER	:	A. Pryor

August 14, 2006

Mail Stop Appeal Brief -Patents
Hon. Commissioner of Patents
P.O. Box 1450
Alexandria, VA 22313-1450

APPELLANTS' CORRECTED BRIEF ON APPEAL PURSUANT TO 37 CFR § 41.37

SIR:

This is an appeal from the final rejection of claims 9, 11, 12 and 15.

(1) REAL PARTY IN INTEREST

The real party in interest is Bayer Aktiengesellschaft by virtue of an assignment recorded in the United States Patent and Trademark Office on September 28, 1993, at Reel 6724, Frame 0495.

(2) RELATED APPEALS AND INTERFERENCES

There are no related appeals or interferences.

(3) STATUS OF CLAIMS

The original submission included a preliminary amendment canceling original claims 1-6 and adding new claims 7-9. The amendment dated February 8, 2002, added new claims 10-14, leaving claims 7-14 then pending. The amendment dated July 18, 2001, added new claim 15, leaving claims 7-15 then pending. The amendment dated May 12, 2004, canceled claims 7, 8, 10, 13 and 14, leaving claims 9, 11, 12 and 15 pending.

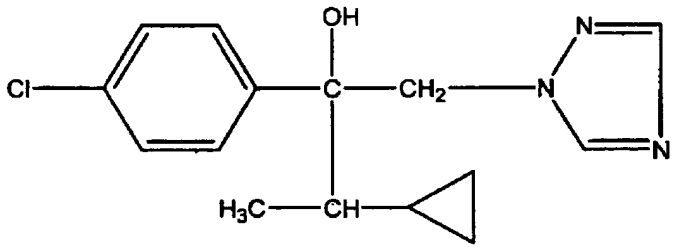
(4) STATUS OF AMENDMENTS

Applicants filed an after-final amendment on February 21, 2006, which contained only argument, and did not change the claims. In the Advisory Action dated March 20, 2006, the Examiner indicated that this amendment had been entered.

(5) SUMMARY OF THE CLAIMED SUBJECT MATTER

There is a single independent claim, viz., claim 15, which relates to an antimicrobial composition comprising a synergistically effective amount therefor of:

a) a first ingredient which is α-(4-chlorophenyl)-α-(1-cyclopropylethyl)-1H-1,2,4-triazole-1-ethanol of the formula (I):



(I)

(cyproconazole) or a metal salt complex or acid addition salt thereof; and

b) a second ingredient, which is an azole selected from the group consisting of tebuconazole and propiconazole.

The compound of the formula (I) (cyproconazole and metal salts and acid addition salts thereof) is described in the instant specification at page 1, lines 9-13, as being useful, in accordance with the present invention, as a microbicide for the protection of industrial materials. At page 9, lines 15 ff, there is the teaching that the compound of formula (I) can be mixed with other antimicrobially active substances, fungicides, etc. At page 9, lines 20-23, there is the teaching that such mixtures can in many cases be synergistic. Tebuconazole and propiconazole are mentioned at page 10, line 10, as formula (I) mixing partners. They are further highlighted as being part of the small group of 25 or so preferred mixing partners at page 15, line 19, continuing to page 16, line 13; see, especially, the last line on page 15. This small group is sufficiently small to constitute a written description of the combination of cyproconazole with each of them.

(6) GROUNDS OF REJECTION TO BE REVIEWED ON APPEAL

I. The rejection of claims 9, 11, 12 and 15 under 35 USC § 103(a) as being obvious over Barnavon et al. ("Barnavon"), US 4,897,427, in view of Valcke, US 5,223,524.

II. The rejection of claims 9, 11, 12 and 15 under 35 USC § 112, first paragraph, for failure to comply with the written description requirement.

III. The rejection of claims 9, 11, 12 and 15 under 35 USC § 112, first paragraph, for failure to satisfy the enablement requirement.

(7) ARGUMENT

I. REJECTION UNDER 35 USC § 103(a)/OBVIOUSNESS

A. THE CITED COMBINATION OF REFERENCES DOES NOT MAKE OUT A *PRIMA FACIE* CASE OF OBVIOUSNESS.

1. BARNAVON DOES NOT TEACH OR SUGGEST A MIXTURE OF CYPROCONAZOLE AND PROPICONAZOLE.

The first statement of this rejection appears to begin at the bottom of page 3 of the Office Action dated February 9, 2005. According to the Examiner:

> "Barnavon teaches a composition comprising cyproconazole. Barnavon teaches the addition of a number of active ingredients to the composition. The actives include propiconazole, prochloraz, hexaconazole, flusilazole, etc. * * * Barnavon does not explicitly show in an Example a composition comprising cyproconazole plus propiconazole or tebuconazole. It would have been obvious to one having ordinary skill in the art to make a composition comprising cyproconazole plus propiconazole or tebuconazole. One would have been motivated to do this since Barnavon suggests the composition comprising cyproconazole plus propiconazole."

Appellants submit that Barnavon does not make out a *prima facie* case of the obviousness of a composition of cyproconazole plus propiconazole. While Barnavon does state a preference for cyproconazole at column 1, lines 53-57, at least in the context of protection against pruning diseases, Barnavon only discloses propiconazole as part of a long list of possible fungicidal mixing partners for cyproconazole at column 5, lines 4 ff, and there is absolutely nothing in Barnavon that highlights the selection of propiconazole from the long list of possible mixing partners, or otherwise would have motivated persons having ordinary skill in the art to select propiconazole for mixing with cyproconazole. Thus, the preferred recitations at column 4, lines 37 ff, while they mention triazoles broadly, mention only hexaconazole specifically, and, moreover, as already acknowledged by the Examiner, none of the 25 working examples mentions a specific combination of cyproconazole and propiconazole.

Appellants respectfully submit that such a "shot-gun" disclosure is manifestly insufficient, as a matter of law, to render *prima facie* obvious a specific combination of

cyproconazole and propiconazole. Although such a combination might well be within the generic teachings of the prior art, as the Examiner suggests, and could have been achieved with the proper selections, a *prima facie* case of obviousness is not made out unless the prior art highlighted these selections in some manner, and, therefore, led persons skilled in the art towards them. *See, In re Baird,* 29 USPQ2d 1550, 1552 (Fed. Cir. 1994) ("The fact that a claimed compound may be encompassed by a disclosed generic formula does not by itself render that compound obvious.") In the instant case, for the reasons advanced above, Barnavon does not highlight the selection of propiconazole, and, thus, of a combination of cyproconazole and propiconazole. Consequently, persons skilled in the art would not have, as a matter of law, have been motivated to prepare such a combination.

2. THE COMBINATION OF BARNAVON AND VALCKE DOES NOT TEACH OR SUGGEST A COMBINATION OF CYPROCONAZOLE AND TEBUCONAZOLE.

According to the Examiner, Valcke teaches the equivalence of propiconazole and tebuconazole, and, therefore, since Barnavon teaches a combination of cyproconazole and propiconazole, the combination of Barnavon and Valcke renders *prima facie* obvious a combination of cyproconazole and tebuconazole substituted for the propiconazole. However, as explained above, Barnavon does not, in fact, teach or suggest any combination of cyproconazole and propiconazole. Consequently, the combination of Barnavon and Valcke likewise fails to teach or suggest any combination of cyproconazole and propiconazole.

3. THE EXAMINER HAS COMPLETELY IGNORED THE POSITIVE CLAIM LIMITATION OF "A SYNERGISTICALLY EFFECTIVE AMOUNT."

According to *Manual of Patent Examining Procedure* ("MPEP") § 2143:

> "To establish a *prima facie* case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. ***Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations.***"

[Emphasis added.]

Claim 15 requires that the recited first and second ingredients be combined in "a synergistically effective amount." This language is a part of the body of claim 15, as it appears after the term "comprising," and, thus, this language cannot be ignored under any theory, for example, that it is preambular, yet the Examiner has completely ignored it. Thus, the Examiner has not pointed to any teaching in either Barnavon or Valcke or their combination that teaches or suggests that a combination of cyproconazole + propiconazole or a combination of cyproconazole + tebuconazole should be synergistic. Valcke does appear to mention that propiconazole and tebuconazole may synergize with one another. However, there is no teaching

or suggestion in either document about any synergistic interaction between cyproconazole, on the one hand, and either propiconazole or tebuconazole, on the other.

Assuming for the sake of argument that the cited references rendered obvious both a combination of cyproconazole + propiconazole and a combination of cyproconazole + tebuconazole, the only thing the Examiner has arguably further established is that such combinations should have an additive effect. Certainly, the Examiner has not established any expectation that either combination should be synergistic. As the instant claims expressly require a synergistic effect, in the form of "a synergistically effective amount," under the best possible viewing of the Examiner's case, he has utterly failed to deal with this positive limitation, and, therefore, has not made out a *prima facie* case of obviousness dealing with ***all*** positive claim limitations as required by law.

B. EVEN IF THE EXAMINER HAS MADE OUT A *PRIMA FACIE* CASE OF OBVIOUSNESS, IT IS REBUTTED BY THE DATA OF RECORD.

Appellants rely on two Rule 132 Declarations of Co-Inventor, Dr. Martin Kugler. The first declaration (hereinafter "the first Kugler declaration") was executed on April 26, 2002, and submitted as a part of the correspondence filed on July 18, 2002. The second declaration (hereinafter "the second Kugler declaration") was executed on December 15, 2005, and submitted as a part of the response filed on February 21, 2006. Copies of both declarations are appended to this Appeal Brief.

The Examiner concedes the data in the declarations prove an unexpected result. Thus, the Examiner writes in the Interview Summary dated December 2, 2005:

> "Examiner explained that an underlining (sic) issue showed ***a narrow range for the unexpected results*** and these was a question whether that data was commensurate in scope with the claims. The examiner suggested that applicants might want to submit additional data supporting the full range of the claims."

[Emphasis added.]

When the Examiner made this statement, only the first Kugler declaration had been filed.

Appellants then set about to provide additional data, and to answer the Examiner's questions, and the result was the second Kugler declaration. Appellants submit that the two Kugler declarations prove an unexpected result, which is indicative of nonobviousness, and, assuming for the sake of argument that the Examiner has established a *prima facie* case of obviousness, such *prima facie* case is rebutted by the two Kugler declarations.

Compared to the first Kugler declaration, the second Kugler declaration includes additional proofs of synergy between cyproconazole, on the one hand, and both propiconazole and tebuconazole, on the other hand. Further, the second Kugler declaration ***contains explanations by the declarant why these data are expected to extend to the entire claimed range.***

In the Advisory Action dated March 20, 2006, the Examiner writes:

> "Dr. Kugler's declaration of synergistic combinations of cyproconazole and propiconazole or tebuconazole is limited to ratios of actives shown in the declarations and ***is not indicative that the combination of actives will be synergistic at all ratios.*** ***For this reason*** Examiner disagrees that the data presented by Dr. Kugler supports the full range of the claims."

[Emphasis added.]

The Examiner's position is completely at odds with the plain language of the declaration itself. At the top of the signature (last) page of the declaration, Dr. Kugler testifies as follows:

> "The foregoing results, in my opinion, provide proof that ***not only the tested ratios, but all ratios*** of cyproconazole and propiconazole and all ratios of cyproconazole and tebuconazole ***would be expected to be synergistic.*** As persons skilled in the art know, *synergism depends on the components that are mixed, not on the ratios of such components.* Accordingly, by showing that cyproconazole and propiconazole and cyproconazole and tebuconazole show synergism at the demonstrated ratios, ***we have, in fact, established the expectation that cyproconazole and propiconazole and cyproconazole and tebuconazole will be synergistic at all ratios."***

[Emphasis added.]

The Examiner has completely and utterly ignored this portion of the second Kugler declaration. Since the claims are not limited to particular mixing ratios of components, they are open to all ratios. The Examiner would apparently have Appellants test at all ratios, which is impossible, or at a representative number, which is possible. The issue here, then, is how much and what type of testing is regarded as being representative. Certainly, the Examiner has some idea or will know it when he sees it. However, Appellants believe the better principle is what persons skilled in the art will accept.

Dr. Kugler has testified, under penalty of perjury, that the data of record are already sufficient to permit a person skilled in the art to the reasonable expectation that all of the claimed ratios are synergistic. While the Examiner retains doubts, he is not himself an expert in the art, nor has he questioned the qualifications of Dr. Kugler, who is an expert in the art. Where, as here, there may be conflict between the Examiner's position and that of an undisputed expert, the Examiner's position must give way. *See, for example, In re Zeidler et al.*, 215 USPQ 490, 494 (CCPA 1982) ("[T]he board * * * erroneously substituted its judgment for that of an established expert in the art.")

Indeed, please see again the Examiner's quote from the Advisory Action dated March 20, 2006. The Examiner gave as "the reason" he was maintaining the rejection that the second Kugler declaration "is not indicative that the combination of actives will be synergistic at all ratios." Clearly, the Examiner is in error since the second Kugler declaration directly addresses this point, and confirms the expectation of persons skilled in the art that all ratios would be expected to be synergistic.

Respectfully, the Examiner has neither established a proper *prima facie* case of obviousness, nor given any good reason why the data of record is inadequate to rebut any *prima facie* case so established. In view of the foregoing, Appellants respectfully submit that this rejection is in error and should be reversed.

II. REJECTION UNDER 35 USC § 112, FIRST PARAGRAPH/ WRITTEN DESCRIPTION

The Examiner found the specification fails to contain a written description of the ratios of components in the two Kugler declarations. The Examiner cites to the issue section of *In re Kollman,* 201 USPQ 193, 194 (CCPA 1979), and argues that "Examples and unexpected results must be in the specification." See, Point I on page 2 of the final rejection. Appellants previously pointed out to the Examiner that this portion of *Kollman* was only the issue section of the case, and not even the holding of the case, and it didn't even say what the Examiner said it did, but the Examiner continues to adhere to this rejection, and his reliance on *Kollman* for support.

Appellants are not aware of any requirement in the law that the specification support unclaimed limitations appearing in a Rule 132 Declaration, and, other than the *Kollman* decision, which does not support such a proposition, the Examiner cites no authority for this apparently new requirement. The written description requirement, by its very terms, requires that the specification contain a written description of "the invention." It is well settled in the patent law that "the invention" is what is claimed. Appellants do not claim the ratios in either Kugler

declaration. Consequently, there is no requirement that the specification contain a written description of these ratios.

III. REJECTION UNDER 35 USC § 112, FIRST PARAGRAPH/ ENABLEMENT

In like manner, 35 USC § 112, first paragraph, requires that the specification enable one of ordinary skill in the art to make and use "the invention." Again, it is well settled in the patent law that "the invention" is what is claimed. Appellants do not claim the ratios in either Kugler declaration. Consequently, there is no requirement that the specification enable one of ordinary skill in the art to make compositions having these specific ratios.

Appellants submit that the invention involves the combination of previously known first and second ingredients, as claimed. Appellants do not believe the Examiner has any doubt that persons skilled in the art should have no difficulty making such combinations. The only problem apparently is that the specific ratios in the two Kugler declarations cannot be found in the specification. Again, as Appellants do not claim these specific ratios, there is no requirement that they appear in the specification.

(8) CONCLUSION

In view of the foregoing, Appellants respectfully request that the Honorable Board reverse the final rejection.

Respectfully submitted,

NORRIS McLAUGHLIN & MARCUS, P.A.

By _____

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(9) CLAIMS APPENDIX

1.-8. (Canceled)

9. (Previously Presented) A method of protecting an industrial material against the deleterious effects of microorganisms, said method comprising applying to said industrial material an amount of the antimicrobial composition according to claim 15 that is effective to protect said industrial material against said microorganisms.

10. (Canceled)

11. (Previously Presented) The antimicrobial composition according to claim 15, wherein the second ingredient is an azole selected from the group consisting of tebuconazole and propiconazole.

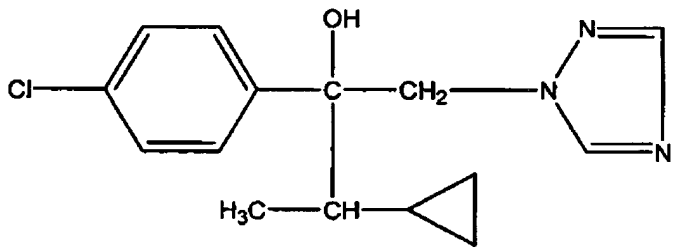
12. (Previously Presented) The antimicrobial composition according to claim 15, wherein the second ingredient is tebuconazole.

13. (Canceled)

14. (Canceled)

15. (Previously Presented) An antimicrobial composition comprising a synergistically effective amount therefor of:

a) a first ingredient which is α-(4-chlorophenyl)-α-(1-cyclopropylethyl)-1H-1,2,4-triazole-1-ethanol of the formula (I):



(I)

(cyproconazole) or a metal salt complex or acid addition salt thereof; and

b) a second ingredient, which is an azole selected from the group consisting of tebuconazole and propiconazole.

(10) EVIDENCE APPENDIX

A. Kugler Declaration executed April 24, 2002

B. Kugler Declaration executed December 15, 2002

(11) RELATED PROCEEDINGS APPENDIX

NONE

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AUG 14 2006

IN THE UNITED STATES PATENTS AND TRADEMARKS OFFICE

APPLICANT: LUTZ HEUER ET AL
SERIAL NO.: 09/901,979
FILED: JULY 10, 2001
FOR: MICROBICIDAL COMPOSITIONS

DECLARATION

I, Martin Kugler, resident at Am Kloster 47, D-42799 Leichlingen, Germany declare:

that I am a biologist having studied at the University of Tübingen;

that I received the degree of doctor rer. nat. at the University of Tübingen in the year of 1986;

that since 1987 I am an employee of Bayer Aktiengesellschaft, Leverkusen, Germany, where I am working in the department of research of technical materials protecting agents located at Krefeld, Germany;

that I am a senior research microbiologist having 16 years experiences in the field of testing and evaluation of chemical compounds for their antimicrobial action;

that I am one of the inventors of the above-identified application;

that the following tests have been carried out under my supervision and direction:

Test 1

Synergism of Cyproconazole / Propiconazole

Pieces of mycelium were punched out of a colony of the wood-destroying fungus **Lentinus tigrinus** and incubated on a nutrient agar containing malt extract/peptone at 26°C. The hyphal growth with and without the addition of the active compound was compared. The minimum inhibitory concentration (MIC) was recorded as the concentration of active compound which completely suppresses radial hyphal growth.

According to the method described by Kull et al. (F.C. Kull, P.C. Eismann, H.D. Sylvestrowicz, R. L. Mayer, Applied Microbiology 9, 538 to 541, 1961) the synergism was then determined. The following equation for the determination of the synergistic index X applies:

$$\frac{Q_A}{Q_a} + \frac{Q_B}{Q_b} = X$$

X = 1 = additivity
X > 1 = antagonism
X < 1 = synergism

Q_a = the MIC of substance A
Q_b = the MIC of substance B
Q_A = the concentration of substance A in the concentration of A/B which suppresses microbial growth
Q_B = the concentration of substance B in the concentration of A/B which suppresses microbial growth

Results:

		MIC
A	cyproconazole	0.5 ppm
B	propiconazole	1 ppm
A/B (1/2)	cyproconazole/propiconazole	0.5 ppm

By using the above values for cyproconazole/propiconazole, mixing ratio of 1:2, the synergistic index X was determined:

$$X = \frac{0.17}{0.5} + \frac{0.33}{1.0} = 0.67$$

Thus, when cyproconazole and propiconazole are mixed in a ratio of 1:2 a high degree of synergism occurs.

Test 2

Synergism of Cyproconazole / Tebuconazole

Pieces of mycelium were punched out of a colony of the wood-destroying fungus **Lentinus tigrinus** and incubated on a nutrient agar containing malt extract/peptone at 26°C. The hyphal growth with and without the addition of the active compound was compared. The minimum inhibitory concentration (MIC) was recorded as the concentration of active compound which completely suppresses radial hyphal growth.

The synergistic index X was determined according to the method described in Test 1.

Results:

		MIC
A	cyproconazole	0.5 ppm
B	tebuconazole	0.3 ppm
A/B (2/1)	cyproconazole/tebuconazole	0.3 ppm

x = 0.73

Thus, when cyproconazole and tebuconazole are mixed in a ratio of 2:1 a high degree of synergism occurs.

Test 3

Synergism of Cyproconazole / copper chloride

Pieces of mycelium were punched out of a colony of the wood-destroying fungi **Coriolus versicolor** and incubated on a nutrient agar containing malt extract/peptone at 26°C. The hyphal growth with and without the addition of the active compound was compared. The minimum inhibitory concentration (MIC) was recorded as the concentration of active compound which completely suppresses radial hyphal growth.

The synergistic index X was determined according to the method described in Test 1.

Results:

		MIC
A	cyproconazole	0.5 ppm
B	copper chloride	>100 ppm
A/B	cyproconazole/copper chloride (1/25)	7 ppm

x = 0.63

The results show that a high degree of synergism occurs when using cyproconazole and copper chloride in a mixing ratio of 1:25 against the wood-destroying fungus Coriolus.

Test 4

Synergism of Cyproconazole / basic copper(II) carbonate

Pieces of mycelium were punched out of a colony of the wood-destroying fungi **Coriolus versicolor** and incubated on a nutrient agar containing malt extract/peptone at 26°C. The hyphal growth with and without the addition of the active compound was compared. The minimum inhibitory concentration (MIC) was recorded as the concentration of active compound which completely suppresses radial hyphal growth.

The synergistic index X was determined according to the method described in Test 1.

Results:

		MIC
A	cyproconazole	0.5 ppm
B	basic copper(II) carbonate	>100
A/B	cyproconazole/basic copper(II) carbonate (1/25)	7

$x = 0.63$

The results show that a high degree of synergism occurs when using cyproconazole and basic copper(II) carbonate in a mixing ratio of 1:25 against the wood-destroying fungus Coriolus.

The undersigned declarant declares further that all statements made herein of his own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that wilful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such wilful false statements may jeopardize the validity of the application or any patent issuing thereon.

Signed at Leverkusen, Germany, this day of 2002-04-24

Martin Kugler

Martin Kugler

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AUG 14 2006

IN THE UNITED STATES PATENTS AND TRADEMARKS OFFICE

APPLICANT: LUTZ HEUER ET AL
SERIAL NO.: 09/901,979
FILED: JULY 10, 2001
FOR: MICROBICIDAL COMPOSITIONS

DECLARATION

I, Martin Kugler, resident at Am Kloster 47, D-42799 Leichlingen, Germany declare:

that I am a biologist having studied at the University of Tübingen;

that I received the degree of doctor rer. nat. at the University of Tübingen in the year of 1986;

that since 1987 I am an employee of Bayer Aktiengesellschaft, Leverkusen, Germany, where I am still working in the department of research of technical materials protecting agents located at Krefeld, Germany;

that I am a senior research microbiologist having 16 years experiences in the field of testing and evaluation of chemical compounds for their action on microbes attacking technical materials;

that I am one of the inventors of the above-identified application;

that the following tests have been carried out under my supervision and direction:

Test 1

Synergism of Cyproconazole / Propiconazole

Pieces of mycelium were punched out of a colony of the wood-destroying fungus **Gloeophyllum trabeum** and incubated on a nutrient agar containing malt extract/peptone at 26°C. The hyphal growth with and without the addition of the active compound was compared. The minimum inhibitory concentration (MIC) was recorded as the concentration of active compound which completely suppresses radial hyphal growth.

According to the method described by Kull et al. (F.C. Kull, P.C. Eismann, H.D. Sylvestrowicz, R. L. Mayer, Applied Microbiology 9, 538 to 541, 1961) the synergism was then determined. The following equation for the determination of the synergistic index X applies:

$$\frac{Q_A}{Q_a} + \frac{Q_B}{Q_b} = X$$

X = 1 = additivity
X > 1 = antagonism
X < 1 = synergism

Q_a = the MIC of substance A
Q_b = the MIC of substance B
Q_A = the concentration of substance A in the concentration of A/B which suppresses microbial growth
Q_B = the concentration of substance B in the concentration of A/B which suppresses microbial growth

Results:

		MIC
A	cyproconazole	0.3 ppm
B	propiconazole	3.0 ppm
A/B	cyproconazole/propiconazole (2:1)	0.3 ppm
A/B	cyproconazole/propiconazole (1:1)	0.5 ppm
A/B	cyproconazole/propiconazole (1:2)	0.5 ppm

By using the above values for cyproconazole/propiconazole

a) for the mixing ratio of 2:1 the synergistic index X was determined:

$$X = \frac{0.2}{0.3} + \frac{0.1}{3.0} = 0.7$$

b) for the mixing ratio of 1:1 the synergistic index X was determined:

$$X = \frac{0.25}{0.3} + \frac{0.25}{3.0} = 0.9$$

c) for the mixing ratio of 1:2 the synergistic index X was determined:

$$X = \frac{0.17}{0.3} + \frac{0.34}{3.0} = 0.7$$

Thus, when cyproconazole and propiconazole are mixed, for example, in a ratio of **2:1, 1:1 and 1:2** a high degree of synergism occurs.

Test 2

Synergism of Cyproconazole / Tebuconazole

Pieces of mycelium were punched out of a colony of the wood-destroying fungus **Gloephyllum trabeum** and incubated on a nutrient agar containing malt extract/peptone at 26°C. The hyphal growth with and without the addition of the active compound was compared. The minimum inhibitory concentration (MIC) was recorded as the concentration of active compound which completely suppresses radial hyphal growth.

The synergistic index X was determined according to the method described in Test 1.

Results:

		MIC	X
A	cyproconazole	0.3 ppm	
B	tebuconazole	0.5 ppm	
A/B	cyproconazole/tebuconazole (2:1)	0.3 ppm	0.86
A/B	cyproconazole/tebuconazole (1:1)	0.3 ppm	0.8
A/B	cyproconazole/tebuconazole (1:2)	0.3 ppm	0.73

Thus, when cyproconazole and tebuconazole are mixed, for example, in a ratio of **2:1, 1:1 and 1:2** a high degree of synergism occurs.

The foregoing results, in my opinion, provide proof that not only the tested ratios, but all ratios of cyproconazole and propiconazole and all ratios of cyproconazole and tebuconazole would be expected to be synergistic. As persons skilled in the art know, synergism depends on the components that are mixed, not on the ratios of such components. Accordingly, by showing that cyproconazole and propiconazole and cyproconazole and tebuconazole show synergism at the demonstrated ratios, we have, in fact, established the expectation that cyproconazole and propiconazole and cyproconazole and tebuconazole will be synergistic at all ratios.

The undersigned declarant declares further that all statements made herein of his own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that wilful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such wilful false statements may jeopardize the validity of the application or any patent issuing thereon.

Signed at Leverkusen, Germany, this day of 2005-12-15

Martin Kugler

Martin Kugler